AD-A172 459 VISCERAL LEISHMANIASIS IN THE GOLDEN HAMSTER AS A MODEL 1/1
FOR HUMAN KALA-AZAR(U) PENNSYLVANIA UNIV PHILADELPHIA
J P FARRELL 27 JAN 83 DAMD17-81-C-1197

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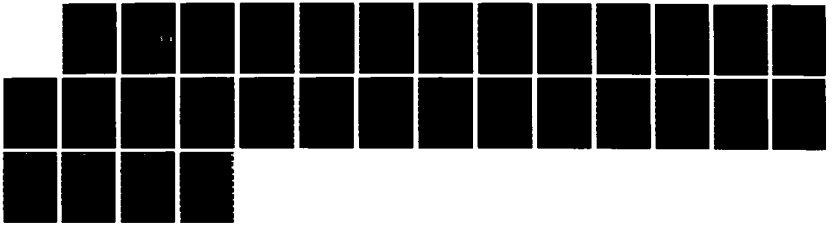

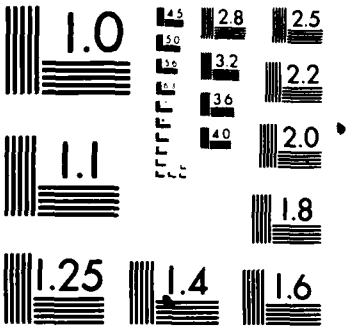

AD-A172 459

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JAN. 27, 1983

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VISCERAL LEISHMANIASIS IN THE GOLDEN HAMSTER AS A MODEL FOR HUMAN KALA-AZAR

Annual Report

January 27, 1983

Jay P. Farrell

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701-5012

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University of Pennsylvania
Philadelphia, Pennsylvania 19104

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SECURITY CLASSIFICATION OF THIS PAGE

Visceral Leishmaniasis in the Golden Hamster

as a Model for Human Kala-azar

Contract - 1197

Annual Progress Report

October 1981-October 1982

Experimental Infections with Various Geographical Isolates of *Leishmania* spp.

A major effort was made during the last year to acquire and establish experimental infections using a variety of *Leishmania* isolates. While some of these recent parasite acquisitions proved non-infective for hamsters, we have succeeded in establishing animal infections with two isolates of *L. infantum* (Greece and France), two isolates of *L. chagasi* (Brazil), one new isolate of *L. donovani* (Kenya), one isolate of unknown identity from natural infections of dogs in Oklahoma, one isolate from Honduras (presumably *L. chagasi*) and two strains of cutaneous origin from South America (*L. mexicana mexicana* and *L. mexicana amazonensis*). These acquisitions complement those strains previously established in our laboratory.

The most interesting of these strains proved to be an isolate from a human case of visceral leishmaniasis in Honduras (Santos Herrera; WR116). When cultured promastigotes of this parasite were inoculated intracardially (IC) into hamsters, infected animals developed heavily parasitized, non-ulcerating cutaneous lesions on the nose, footpads and genitals. Only low numbers of visceral parasites were detected by impression smears of the spleen and bone marrow. Subsequent parasite inoculations into hamsters, using either amastigotes isolated from dermal lesions in hamsters or cultured promastigotes grown from splenic isolates, produced similar cutaneous infections. Since Santos Herrera exhibited such strong dermatropic tendencies, it was next inoculated intradermally (ID) into BALB/c mice. The resultant course of infection, as shown in Figure 1, is

typical of that seen with L. tropica or with a variety of parasites of the L. mexicana complex.

These studies suggested that this human visceral isolate was really a cutaneous strain which could potentially cause visceral infections in man. To test the relationship of Santos Herrera to known cutaneous parasites, a cross-protection study was run against a defined cutaneous species. C57BL/6 mice were inoculated intradermally with 1 x 10^6 amastigotes of a relatively nonvirulent strain of L. mexicana amazonensis. After resolution of infection (6 weeks) healed and control mice were injected ID with 10^7 amastigotes of either L. mexicana mexicana or Santos Herrera. As might be expected, L.m. amazonensis provided some protection against L. m. mexicana. In addition, L.m. amazonensis also protected against chronic infection with Santos Herrera (Figure 2). These studies revealed another characteristic of the Honduran isolate: following ID inoculation into C57BL/6 mice, the parasites induced a primary ulcer which appeared to heal, only to relapse and cause large, non-healing cutaneous lesions. Since prior exposure to L. m. amazonensis provided protection against relapsing, but not primary, lesions with Santos Herrera, it is unlikely that these two parasites are identical. However, the clinical protection afforded by the L. mexicana amazonensis strain does provide a basis for future studies aimed at protecting animals against more virulent visceral or non-healing cutaneous strains following exposure to purely cutaneous strains of low virulence.

An effort has been made to identify the Santos Herrera isolate by sending the organism to Dr. Diane McMahon Pratt for monoclonal antibody typing. Previous typings by radiorespirometry and isozymes do not agree as to the cutaneous or visceral origin of this organism. If the parasite is L. chagasi, then it certainly behaves differently form other L. chagasi isolates from Brazil which, in this laboratory, produce classical visceral

infections in hamsters.

In addition to studies with the Santos Herrera strain, we have also run a few preliminary infections with a strain of L. infantum (WR438) which was isolated from a Boston dog following travel to Greece. This strain is purely viscerotropic and produces systemic infections similar to L. donovani following IC inoculation into hamsters, although this parasite appears to proliferate at a slower rate than our reference strain, L. donovani (2S) from the Sudan. Following intradermal inoculation, animals given 438 strain amastigotes exhibited a similar degree of resistance to challenge with the 2S strain as to a homologous 438 challenge, suggesting an antigenic relationship between organisms causing visceral infection in Greece and the Sudan (see Figure 3).

We have also run one course of infection study comparing strain 438 with a strain of L. infantum isolated from a human case of visceral leishmaniasis in France (WR:351). Liver parasite burdens from infected animals were as follows:

	Day 1	Day 16	Day 35
Strain 438	1.02×10^7	7.1×10^8	1.2×10^9
Strain 351	1.04×10^7	2.1×10^7	2.4×10^7

These hepatic parasite numbers suggest that the 351 strain grows at a very slow rate in vivo when compared to the 438 strain. Whether or not this is an intrinsic characteristic of the parasite is yet to be determined since this organism had only been passaged once through hamsters prior to the above course of infection study. Additional animal passages may increase the virulence (eg. growth rate) of this strain.

Immunity to L. donovani in the Golden Hamster

Much of our effort during the past year concentrated on the study of immunological responses in hamsters infected with the 2S (Sudan) strain of L. donovani. Briefly, we have utilized three model systems:

1) I C infections - Inoculation of 1-10 x 10^6 amastigotes intracardially results in a progressive visceral disease in which parasites multiply unchecked in spleen and liver tissue, and death ultimately results from a fulminating infection.

2) I D infections - Inoculation of 1-10 x 10^6 amastigotes intradermally into hamsters results in transient dermal lesions which usually resolve within 6-8 weeks. These animals display significant acquired resistance to reinfection.

3) I D - I C Challenge infections - Inoculation of 1-10x10^6 amastigotes ID followed several weeks later by an IC challenge with similar numbers of organisms results in visceral infections in which splenic and hepatic parasite burdens are significantly lower than those seen in primary IC infections. Acquired resistance is not absolute, however, since parasite numbers eventually increase and animals ultimately succumb to infection.

Preliminary studies in these model systems compared the response to Con A of spleen cells from normal hamsters with spleen cells from hamsters inoculated IC with 1 x 10^6 amastigotes. Since previous studies in this laboratory had demonstrated an indomethacin-sensitive, nonspecific suppressor cell in mice infected with L. tropica (Scott and Farrell, J. Immunol. 127:2395, 1981), the effect of indomethacin on hamster responses was also assessed. The results from an 8 week course of infection are summarized in Table 1. Briefly, spleen cells from IC inoculated animals show a depressed ability to respond to Con A as the infection progresses. In this particular study, markedly lower Con A responses were seen at 4 weeks of infection, at which time proliferative responses were partially reversed by indomethacin. Spleen cells from hamsters infected for 6-8 weeks are almost totally nonresponsive to Con A and these depressed responses were not augmented by indomethacin. Since other studies

from this laboratory have demonstrated an adherent splenic macrophage from viscerally infected hamsters which suppresses antibody production to sheep RBCs in vitro, it is possible that a similar cell also suppresses cell proliferation to mitogens. Some evidence for this is seen in Table 2 which shows that removal of phagocytic cells by carbonyl iron treatment enhances depressed Con A responses. Since macrophages are a major source of prostaglandins, it is likely that the onset of indomethacin-reversible depression is related to an influx of macrophages into the spleen and is associated with splenic hyperplasia during infection. The failure of indomethacin to influence responses at 6 or 8 weeks may suggest additional suppressor mechanisms or else altered T cell levels and/or function during this stage of the disease.

In a related experiment, we also compared Con A responses by spleen cells from IC vs ID infected hamsters. As seen in Table 3, only the IC spleen cells show depressed responses to this mitogen; ID spleen cell responses are similar to controls.

Since the primary emphasis of this work is to investigate parasite-specific immunological responses, we have also assayed antigen-specific proliferative responses in experimentally infected animals. The antigen for these studies was prepared by sonically disrupting L. donovani (2S) promastigotes. As seen in Table 4, spleen cells from IC inoculated hamsters develop a transient antigen-specific response which was present at 2 weeks but disappeared by 4 weeks of infection. Since background thymidine uptake varied among infected animals, results are presented as both ΔCPM and stimulation indices (a stimulation index of less than 2 is not significant). Indomethacin had no appreciable effect on antigen-specific responses.

The most interesting results from this series of experiments came from a comparison of proliferative responses in ID, IC, and ID-IC challenged hamsters.

Table 5 shows relative visceral parasite burdens in these groups of animals. As expected, ID parasite inoculation did not result in significant levels of hepatic parasites. IC injections, however, produced a typical visceral course of infection with a rapid increase in hepatic parasite numbers. As predicted, exposure to a prior ID infection led to some acquired resistance as evidenced by significantly lower hepatic parasite burdens in the ID-IC challenged group.

The proliferative responses to Con A by spleen and lymph node cells from these three groups are shown in Table 6. As previously described, Con A responses by spleen cells from ID infections are normal, whereas those from IC infections are depressed. Of interest is the observation that lymph node cells from the IC infected group remained responsive to Con A, which suggests that depression is limited to heavily parasitized tissues such as the spleen. It also appears that a relative state of resistance, as is seen in the ID-IC challenged group, does not prevent nonspecific immunodepression in the spleen. This is, perhaps, not surprising, since splenic hyperplasia in this group is similar to that in animals receiving only an IC infection (data not shown).

However, when antigen-specific responses were assessed, the results indicated that an antigen-specific suppressor cell may be operating in these systemically infected animals. The results, in Table 7,show that lymph node cells from ID-IC challenged animals did not respond to antigen, even though they did respond to Con A. Since the prior ID infection would provoke a strong, antigen-specific proliferative response, we must assume that the IC challenge induces active suppression of this response. Since non-specific suppression appears to be limited to the spleen, it is likely that parasite-specific suppression is due to a circulating suppressor cell rather than to suppressor macrophages which develop and reside in parasitized spleen.

In addition to proliferative responses, we have also followed DTH responses in infected animals. The antigen used in these studies was phenol-saline-killed promastigotes (leishmanin). The results, shown in Table 8, have been difficult to interpret. Animals inoculated ID appear to consistently respond to leishmanin with footpad swelling which peaks at 24 hrs and remains high through 48 hrs. Animals infected by the IC route show marked footpad responses at 24 hrs but minimal 48 hr responses. These animals also exhibit strong Arthus (6 hr) responses. Animals with ID infections followed by an IC challenge appear to have significant 48 hr responses; however, we have been able to consistently detect live amastigotes within the leishmanin-injected footpads of these animals. It is probable that these parasites have been recruited to the skin-test site, possibly within mononuclear cells from the bone marrow. Their presence complicates the interpretation of skin test results since live organisms might affect the type and degree of inflammatory response. This problem will be addressed in our renewal proposal.

In addition to the above progress, we wish to reiterate the results of two previous experiments, since they will provide the basis for studies proposed in our renewal application. The first of these studies examined dose and timing effects of cutaneous infections on resistance to IC challenge infections. Briefly, hamsters were inoculated ID with either 1.5×10^5 or 1.5×10^6 L. donovani amastigotes. Groups of these ID inoculated hamsters, as well as normal control animals, were then challenged IC with 1×10^7 organisms at 1,2,3 or 4 weeks after the ID infections. Animals were sacrificed 10 days after challenge to determine parasite burdens. As shown in Figure 4, the ID inoculated animals showed increasing resistance to an IC challenge through the first 4 weeks of infection, with higher numbers of organisms administered intradermally producing a greater level of resistance.

A second experiment was performed to test if drug-cure of active visceral infections would enhance resistance to an IC challenge infection. Hamsters were first inoculated with 1 x 10^6 parasites by either an intracardial or intraperitoneal route. At three weeks, these infected animals, as well as controls, received Pentostam (180 mg/kg IP) daily for 14 days. Thirty-five days after the end of drug treatment, all animals were challenged IC with approximately 5 x 10^6 amastigotes and sacrificed 11 days later for the determination of levels of visceral parasitization. The results, in Figure 5, show that the IP infected, drug-treated hamsters showed a substantial reduction in parasite numbers when compared with controls. The IC infected, drug-treated group did not show similar evidence of resistance to infection. The reasons for these different effects are unclear; however, they do suggest the IP inoculated animals are able to generate some resistance if the infection is terminated during its early stages. Further studies will be proposed to investigate immunological responses in these animals following cure of systemic infection.

FIGURE 1

Course of infection of Santos Herrera strain in
BALB/c mice following ID inoculation with 1 x 10^7 promastigotes

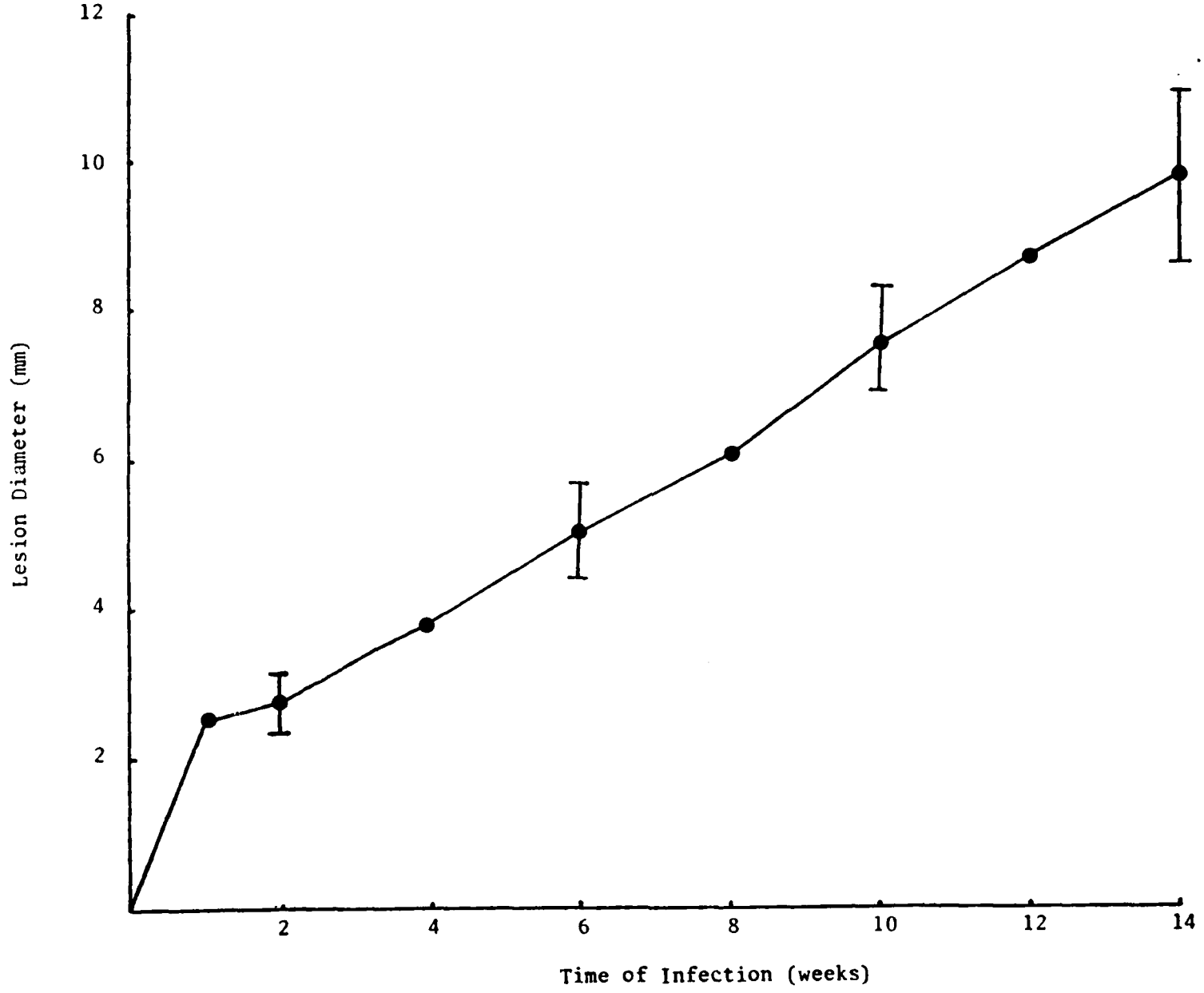

FIGURE 2

C57BL/6 mice infected ID with L.m. amazonensis and challenged ID at 7 weeks with (a) Santos Herrera or (b) L.m. mexicana

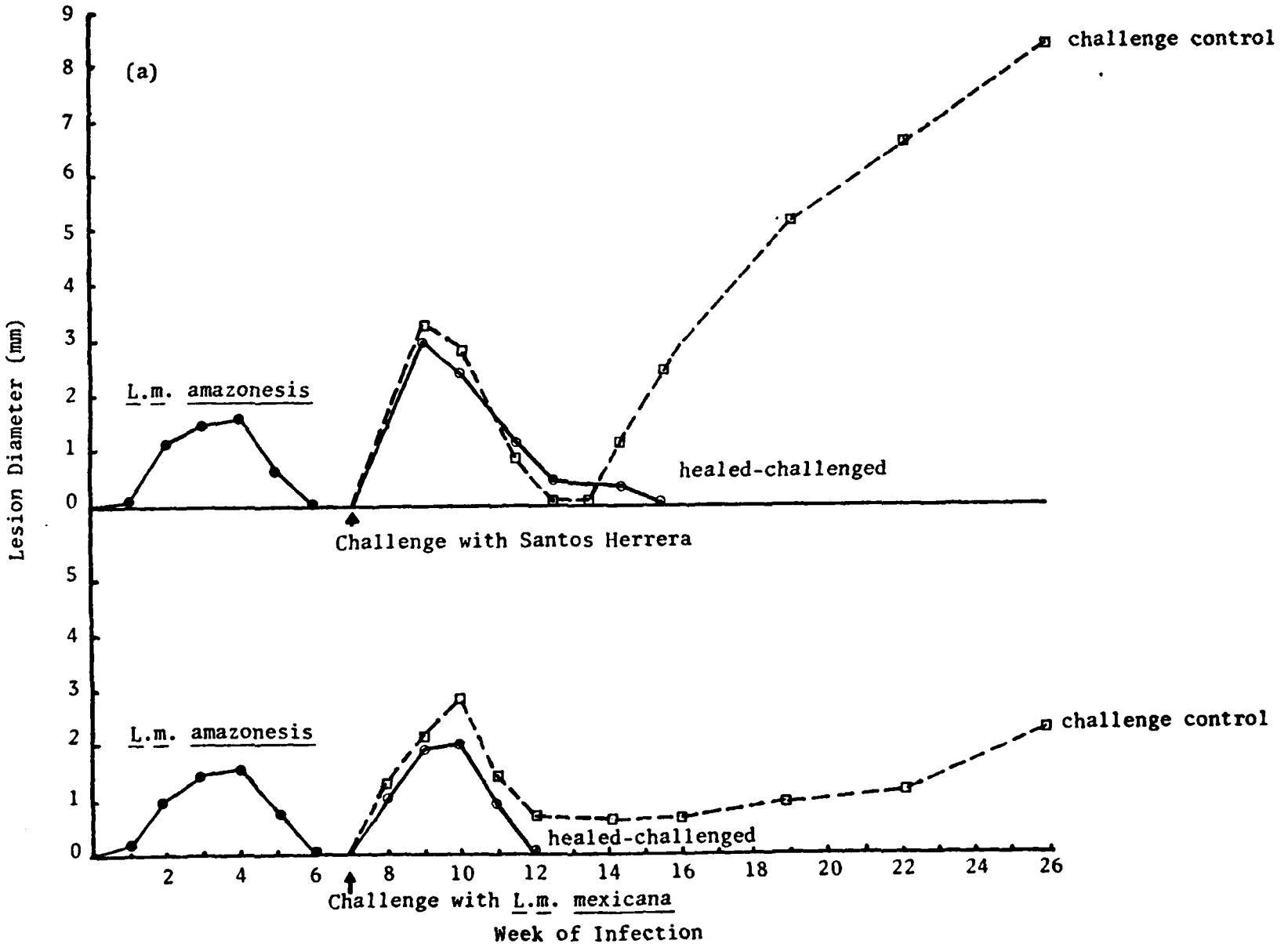

FIGURE 3

Cross protection between
L. infantum (438) and L. donovani (2S)

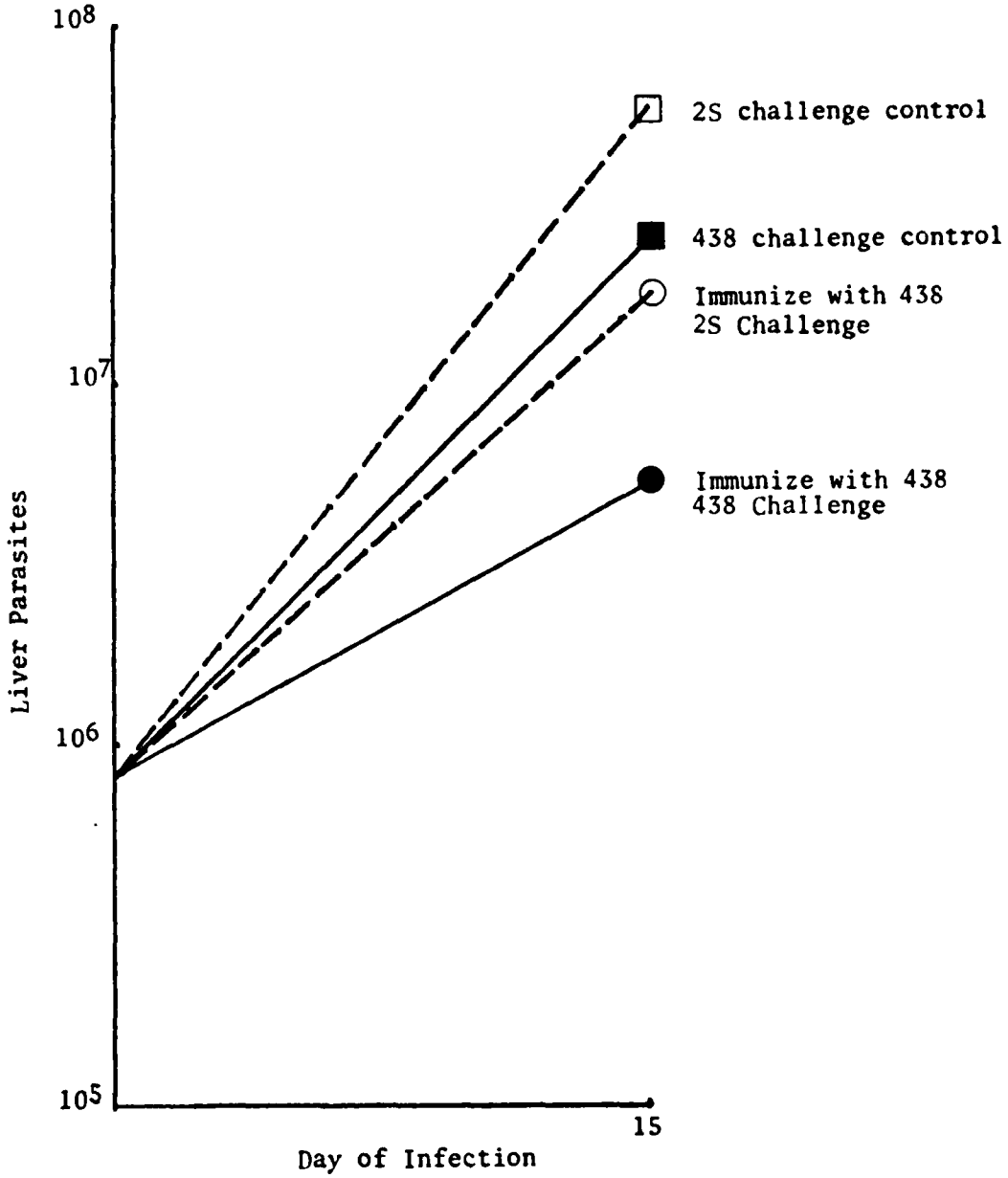

FIGURE 4

EFFECT OF DOSE VS. TIME OF INTRADERMAL

INFECTION ON ACQUIRED RESISTANCE

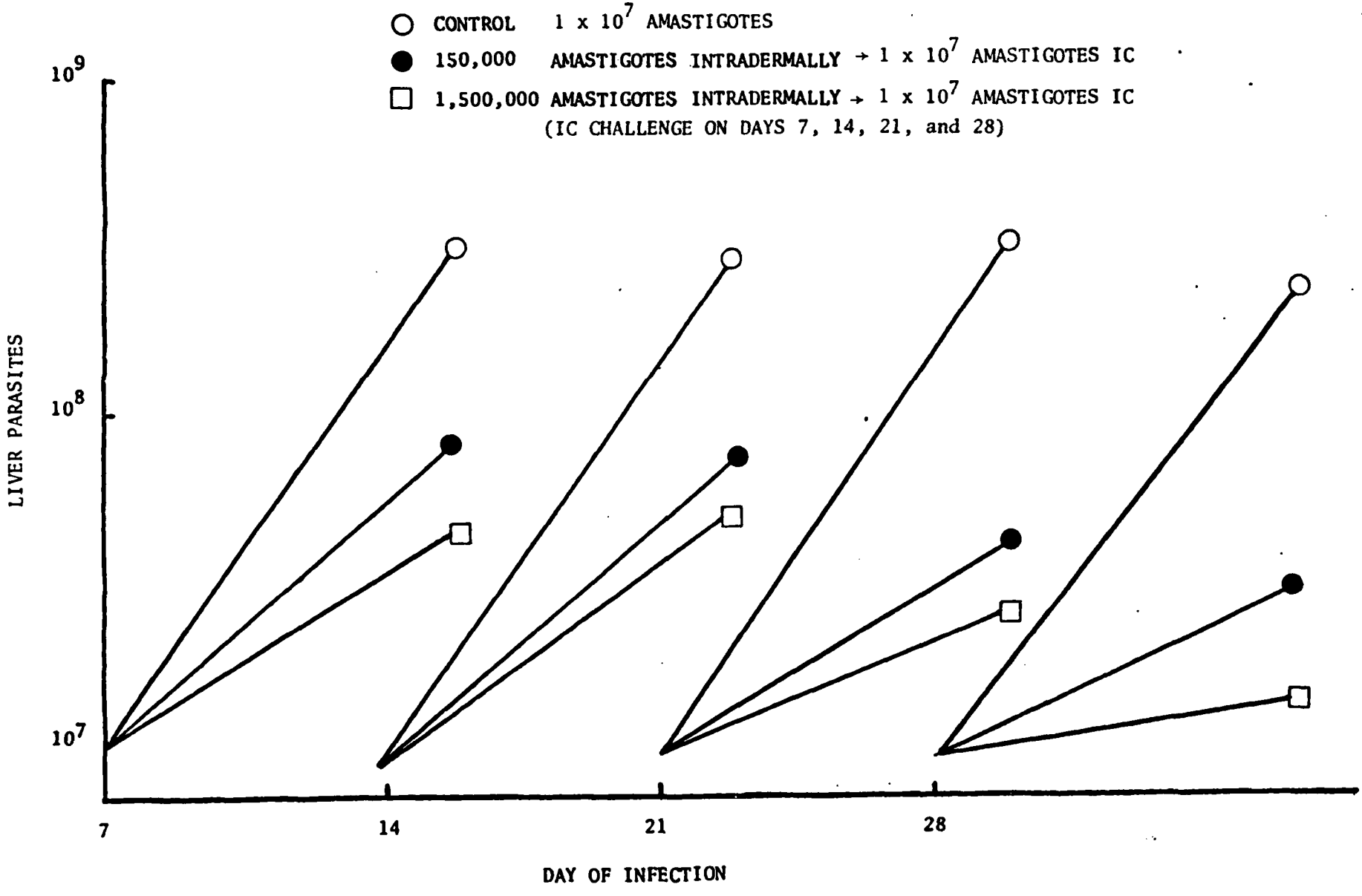

FIGURE 5

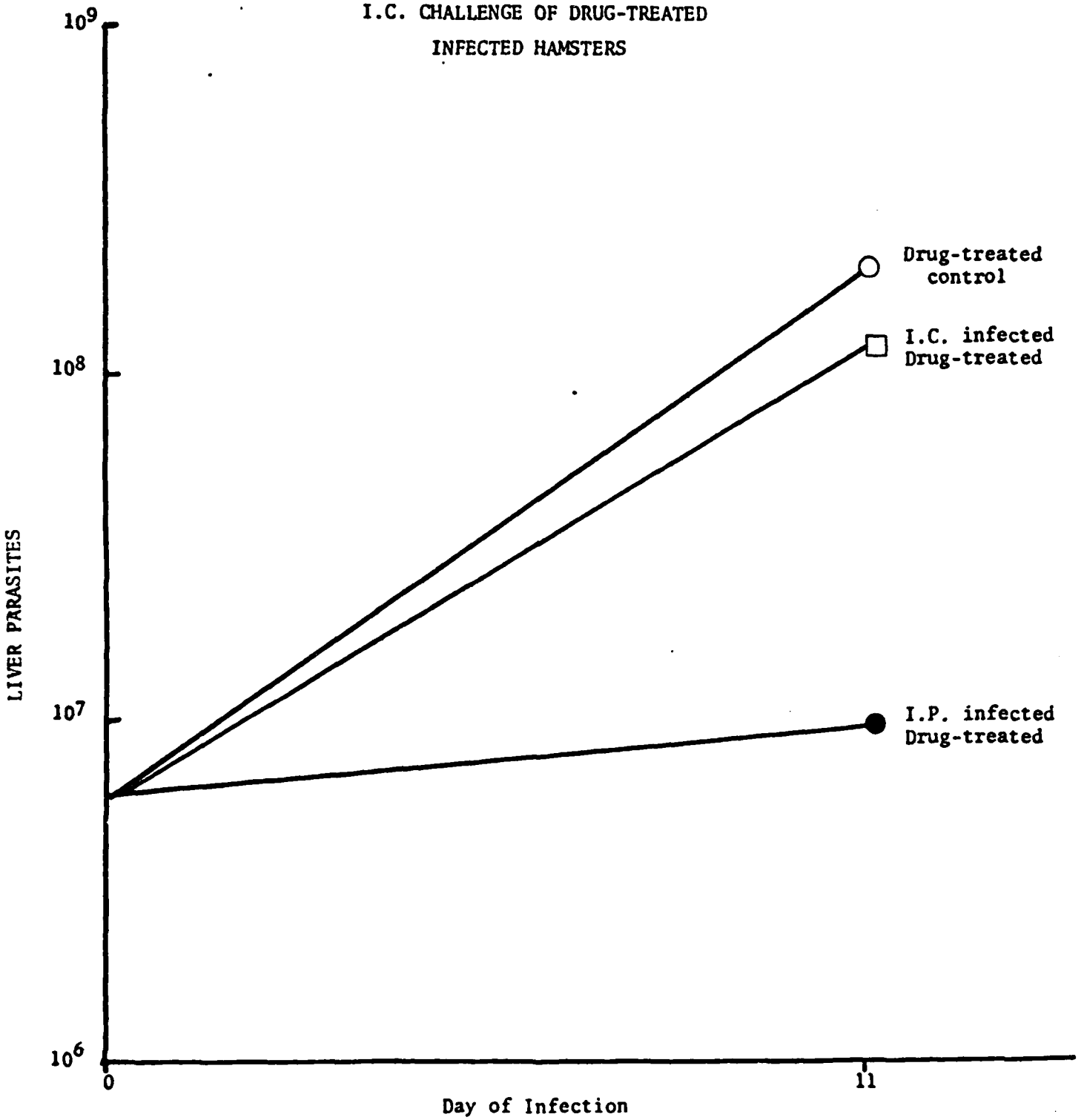
I.C. CHALLENGE OF DRUG-TREATED
INFECTED HAMSTERS
10^9
10^8
10^7
10^6
LIVER PARASITES
Drug-treated control
I.C. infected Drug-treated
I.P. infected Drug-treated
0
11
Day of Infection

Table 1. Effect of Indomethacin on Con A responses by spleen cells from hamsters infected with Leishmania donovani.

Week of Infection	Indomethacin	Con A Response (ΔCPM)*
0	-	74,362
	+	83,043
2	-	48,914
	+	61,416
4	-	10,358
	+	32,341
6	-	3,856
	+	5,799
8	-	1,050
	+	1,674

* ΔCPM = Stimulated CPM - background CPM

Table 2. Effect of carbonyl iron treatment on Con A responses by spleen cells during visceral infection.

Duration of Infection(wk)	Spleen Con A Response (% of Control)	Response After Carbonyl Ion Treatment (% of Control)
1	93%	94%
3	59%	71%
5	28%	59%

Table 3. Con A responses by spleen cells in normal, ID and IC infected hamsters

Week of Infection	Indomethacin	Con A Response (CPM)		
		Normal	ID Infected	IC Infected
2	-	68,356	63,840	31,397
	+	74,974	57,003	37,272
4	-	50,630	57,240	3,104
	+	55,443	60,543	5,013
6	-	52,932	62,341	2,337
	+	50,098	64,291	3,242

Table 4. Effect of indomethacin on antigen specific responses by spleen cells from hamsters infected with Leishmania donovani

Week of Infection	Indomethacin	Antigen (4 μg/ml) Response (ΔCPM)	Stimulation* Index
0	-	1,574	1.1
	+	2,040	0.9
2	-	24,019	13.3
	+	24,299	14.6
4	-	3,195	1.21
	+	9,921	1.78
6	-	3,767	2.24
	+	3,403	1.83
8	-	2,692	1.29
	+	8,510	1.27

* $\frac{\text{CPM with Ag}}{\text{CPM without Ag}}$

Table 5. Mean liver parasite burdens in control and resistant hamsters

Week of Infection	ID*	IC**	ID -- IC challenge***
2	none detected	80×10^6	7×10^6
4	none detected	270×10^6	22×10^6
6	none detected	1060×10^6	82×10^6

* 5×10^6 amastigotes ID

** 1×10^7 amastigotes IC

*** 5×10^6 amastigotes ID followed at least 3 weeks later with 1×10^7 amastigotes IC

Table 6. Comparison of Con A responses in ID,IC, and IC-challenged hamsters.

Week after IC Challenge	Cell Type	Con A Responses (ΔCPM) ID*	IC → ID**	IC***
2	Spleen	63,881	6,963	2,680
	Lymph Node	69,252	38,610	54,311
4	Spleen	55,884	4,089	3,121
	Lymph Node	57,683	54,487	51,258
6	Spleen	61,198	3,558	3,269
	Lymph Node	70,215	53,614	60,691

* Inoculated intradermally with 5 x 10^6 amastigotes

** ID inoculated hamsters challenged at 3 weeks with 1 x 10^7 amastigotes via intracardial inoculation

*** Intracardial challenge only

Table 7. Comparison of antigen-specific proliferative responses in ID, IC, and ID-challenge hamsters

Week after IC Challenge	Cell Type	Antigen (ΔCPM) ID*	ID → IC**	IC***
2	Spleen	31,883	3,947	19,312
	Lymph Node	41,027	5,580	862
4	Spleen	22,014	2,497	1,114
	Lymph Node	21,800	4,517	887
6	Spleen	31,620	1,113	2,149
	Lymph Node	16,432	3,609	1,497

* Inoculated intradermally with 5×10^6 amastigotes

** ID inoculated hamsters challenged at 3 weeks with 1×10^7 amastigotes via intracardial inoculation

*** Intracardial challenge only

Table 8. Skin test responses to Leishmanin in hamsters infected with L. donovani*

Week of Infection	ID Infection		IC Infection		ID - Challenged	
	24hr	48hr	24hr	48hr	24hr	48hr
1	0.60	0.75	0.80	0.50	0.55	0.50**
2	0.75	0.85	1.00	0.30	0.40	0.75**
4	1.30	0.80	1.35	0.50	0.25	0.55**
6	0.75	0.80	0.85	0.30	1.05	0.80**

* Difference in foot pad thickness (footpad leishmanin - footpad with phenol saline) Swelling > 0.5 mm is considered a specific response

** Amastigotes detected from footpad at leishmanin challenge site

Dr. Jay P. Farrell

U.S. Army

From 10/1/81 Through 11/30/82

Budgeted Categories	Current Budget	Actual Expenditures Thru 12/31/81	Est. Costs for Remainder of Current Budget Period	Total Estimated Expenditures	Estimated Unexpended Funds
Personnel	15,070	14,661	409	15,070	0
Benefits	3,667	3,564	103	3,667	0
Supplies	18,521	10,523	2,700	13,223	5,298
Repair	600	576	24	600	0
Equipment	7,615	7,035	0	7,035	580
Publication	250	0	0	0	250
Misc.	7,960	4,652	0	4,652	3,308
Animal Care	8,170	13,829	3,777	17,606	(9,436)
Indirect Costs	37,529	31,074	6,455	37,529	0
Total	$99,382	$85,914	$13,468	$99,382	$ 0

S Wade

DISPOSITION FORM

For use of this form, see AR 340-15 the proponent agency is TAGO. S: 18 February 1983

REFERENCE OR OFFICE SYMBOL	SUBJECT
SGRD-RMS	Review of Progress/~~Final~~ Report, 27 Jan 83 (Dec 31 - Dec 82)

TO WRAIR/Dr. Howard Noyes FROM SGRD-RMS DATE 3 February 1983 CMT 1
Mrs. Idoine /jkp/7325

1. Attached is draft Progress/~~Final~~ Report on Contract/~~Grant~~ No. DAMD17-81-C-1197
(Institution) University of Pennsylvania, Philadelphia, PA 19104
by (Prin Inv) Jay P. Farrell

2. Request scientific evaluation and completion of CMT 2.

3. Are there any developments described or alluded to in the report that you feel might be patentable? _____(yes) _____(no) If so, please immediately contact the appropriate Contracting Officer's Representative in the Acquisition Division.

1 Incl
as

Jane Idoine
Scientific and Technical Information Division

FROM Project Officer DATE 23 March 1983 CMT 2

TO SGRD-RMS/Madigan

1. Referenced report has been reviewed. It (is) (~~is not~~) considered scientifically acceptable.

2. Report is not scientifically acceptable for the following reasons:

3. SUMMARY OF RESULTS: (prepared for Final Grant reports only). (Use additional sheet, if needed.)

1 Incl
as

/s/ Howard E. Noyes
PROJECT OFFICER

TO SGRD-RMA FROM SGRD-RMS DATE April 26, 1956 CMT 3

1. Referenced report has been reviewed for both scientific and administrative requirements.

2. It (is) (is not) scientifically acceptable. (Comments of Project Officer are furnished for your information.)

3. It (is) (is not) administratively acceptable. (See copy of attached letter to contractor/grantee.)

1 Incl
as

Virginia M McCa
Scientific and Technical Information Division

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REFERENCE OR OFFICE SYMBOL	SUBJECT
SGRD-UWM-B	Review of Progress Report

Assoc Dir Rsch Mngt
WRAIR
DR. Noyes

FROM CPT McGREEVY
COTR

DATE 18 March 1983

CMT 1

1. The following contract is reviewed:
Principal Investigator: Dr. Jay P. Farrell
Title: Visceral Leishmaniasis in the Golden Hamster as a Model for Human Kala-Azar
Contract NO: DAMD17-81-C-1197

2. During the contract period the PI proposed to survey a number of Leishmania strains for their ability to infect the skin of hamsters and disseminate to the spleen, liver and bone marrow. About a dozen strains were studied. In each case, amastigotes produced a transient infection in the skin which self-cured and failed to visceralize.

3. The PI proposed to determine if a transient dermal infection protects against an IC challenge of L. donovani. Vaccinating dermal infections stimulated protective immunity as there was 90% suppression of the IC challenge compared to non-vaccinated controls. The degree of protection was related to dose and timing effects. Vaccination with 1.5×10^6 amastigotes produced better immunity than vaccination with 1.5×10^4 amastigotes. Better protection was obtained when the animals were challenged on day 28 relative to days 1, 14 and 21.

4. The PI also found that protecton to L. donovani could be stimulated by infecting the hamsters IP and terminating this infection with Pentostam.

5. Immunologic studies on visceral leishmaniasis showed that IC infections led to the generation of suppressor cells while ID infections led to protective immunity without the generation of suppressor cells.

6. With respect to cutaneous Leishmaniasis the PI found that L. M. amazonesis produces a transient infection in the skin of C57BL/6 mice. Healed mice were protected against a homologous challenge, but failed to resist a heterologous challenge.

7. The PI has been most productive and has generated promising results. The major point is that the route of inoculation determines the outcome of infection, i.e., suppression or protection. These studies will serve as the basis for development of a human vaccine. Continued support is encouraged.

Patrick B McGreevy

PATRICK B. Mc GREEVY, Ph.D.
CPT, MSC
Chief, Leishmania Section
Department of Parasitology
Division of Experimental Therapeutics
WRAIR

DISPOSITION FORM

For use of this form, see AR 340-15; the proponent agency is TAGO. S: 18 February 1983

REFERENCE OR OFFICE SYMBOL	SUBJECT
SGRD-RMS	Review of Progress/~~Xxxxx~~ Report, 27 Jan 83 (Dec 81 - Dec 82)

TO WRAIR/Dr. Howard Noyes FROM SGRD-RMS DATE 3 February 1983 CMT 1
Mrs. Idoine /jkp/7325

1. Attached is draft Progress/~~Xxxxx~~ Report on Contract/~~Xxxxx~~ No. DAMD17-81-C-1197
(Institution) University of Pennsylvania, Philadelphia, PA 19104
by (Prin Inv) Jay P. Farrell

2. Request scientific evaluation and completion of CMT 2.

3. Are there any developments described or alluded to in the report that you feel might be patentable? _____(yes) X (no) If so, please immediately contact the appropriate Contracting Officer's Representative in the Acquisition Division.

1 Incl
as

Jane Idoine
Scientific and Technical Information Division

FROM Project Officer DATE 23 March 83 CMT 2

TO SGRD-RMS/Madigan

1. Referenced report has been reviewed. It (is) (~~is not~~) considered scientifically acceptable.

2. Report is not scientifically acceptable for the following reasons:

3. SUMMARY OF RESULTS: (prepared for Final Grant reports only). (Use additional sheet, if needed.)

1 Incl
as

Howard E. Noyes
PROJECT OFFICER

TO SGRD-RMA FROM SGRD-RMS DATE Sept 16, 1983 CMT 3

1. Referenced report has been reviewed for both scientific and administrative requirements.

2. It (is) (is not) scientifically acceptable. (Comments of Project Officer are furnished for your information.)

3. It (is) (is not) administratively acceptable. (See copy of attached letter to contractor/grantee.)

1 Incl
as

Virginia M. McCabe
Scientific and Technical Information Division

DA FORM AUG 80 2496 PREVIOUS EDITIONS WILL BE USED

DISPOSITION FORM

For use of this form, see AR 340-15; the proponent agency is TAGO.

REFERENCE OR OFFICE SYMBOL	SUBJECT
SGRD-UWM-B	Review of Progress Report

TO Assoc Dir Rsch Mngt
WRAIR
DR. Noyes

FROM CPT McGREEVY
COTR

DATE 18 March 1983

CMT 1

1. The following contract is reviewed:
Principal Investigator: Dr. Jay P. Farrell
Title: Visceral Leishmaniasis in the Golden Hamster as a Model for Human Kala-Azar
Contract NO: DAMD17-81-C-1197

2. During the contract period the PI proposed to survey a number of Leishmania strains for their ability to infect the skin of hamsters and disseminate to the spleen, liver and bone marrow. About a dozen strains were studied. In each case, amastigotes produced a transient infection in the skin which self-cured and failed to visceralize.

3. The PI proposed to determine if a transient dermal infection protects against an IC challenge of L. donovani. Vaccinating dermal infections stimulated protective immunity as there was 90% suppression of the IC challenge compared to non-vaccinated controls. The degree of protection was related to dose and timing effects. Vaccination with 1.5×10^6 amastigotes produced better immunity than vaccination with 1.5×10^4 amastigotes. Better protection was obtained when the animals were challenged on day 28 relative to days 1, 14 and 21.

4. The PI also found that protecton to L. donovani could be stimulated by infecting the hamsters IP and terminating this infection with Pentostam.

5. Immunologic studies on visceral leishmaniasis showed that IC infections led to the generation of suppressor cells while ID infections led to protective immunity without the generation of suppressor cells.

6. With respect to cutaneous Leishmaniasis the PI found that L. M. amazonesis produces a transient infection in the skin of C57BL/6 mice. Healed mice were protected against a homologous challenge, but failed to resist a heterologous challenge.

7. The PI has been most productive and has generated promising results. The major point is that the route of inoculation determines the outcome of infection, i.e., suppression or protection. These studies will serve as the basis for development of a human vaccine. Continued support is encouraged.

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WRAIR

END

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DTIC